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Regulating in Developing Countries: Multiple Roles for Medical Research and Products Regulation in Argentina and India

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Abstract: This paper engages with the complex relationship between innovation and human health and the role of regulation in bringing the two together, and, in doing so, facilitating inclusive innovation in emerging economies. After outlining the contested role of regulation, we provide two case studies: regenerative medicine regulation in Argentina, and medical devices regulation in India. While these empirically-based case studies examine different scientific sectors in different jurisdictions and therefore have different contextual foundations, they demonstrate the important link between regulatory policies and the successful promotion of innovation. Through them we challenge the oft-repeated complaint that regulation stifles innovation, demonstrating that both a lack of regulation (Argentina) and poorly conceived regulation (India) are equally damaging to innovation, to actor wellbeing, and, ultimately, to human health. We argue that devising new forms of regulation can facilitate increased innovation and thus improved technological (and economic) competitiveness (ie: social/regulatory innovation can lead to improved technological/scientific innovation).

Keywords: regulation, governance, innovation, regenerative medicine, medical devices, Argentina, India

1. Introduction

A range of sectors, activities, and technologies rely on the biosciences, which are increasingly important for translating technical knowledge into useful products, including ‘bioproducts’ (i.e., products that interact with the biological and which might be administered within the clinical or consumer context). The biosciences and their resultant biotechnologies are integral to the ‘bioeconomy’, which, though somewhat amorphous, describes the commercial value of, and activities around, biological knowledge and bioproducts, and it is tangled up with the concept of ‘innovation’. Sometimes defined as ‘the successful application of new idea to use’ (Kaplinksy and Morris, 2008), innovation is the lode-stone of the ‘creative destruction’ claimed by Schumpeter (1934, 1942) as necessary for economic development.¹ Successful innovation

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¹ Innovation can be ‘path-breaking’ or ‘path-following’. The former involves changes deemed to be radical or disruptive), whereas the latter, which is more common, relies on small or incremental developments in products

requires appropriate linkages between diverse (and often networked) actors, effective nodes for consideration of the myriad social concerns and technical hurdles, and space to forge unique or alternative practices and processes that are necessary to transform new ideas into safe and effective products. Governments seek to encourage these phenomena through industrial policies, infrastructure investment, taxation, and regulation.²

This paper focuses on the last strategy, regulation, and more particularly regulation in the health technologies setting. While regulation is often not the *main* driver of innovation or healthcare system evolution (Wolf and Delgado, 2003), it can have profound impacts on stakeholder ambitions and activities, and therefore on innovation, on institutional formation, and on knowledge-deployment within healthcare systems. It can influence (and sometimes determine) the types of enterprises that succeed, the types of knowledge that get privileged, and the types of structures that evolve, and so impact on the dynamism of whole disciplines or sectors (Tait, 2007). Indeed, regulation has been described as a powerful determinant of what we even consider to be ‘innovative’ (Bud, 1999). In short, regulation can be an important feature of both the innovation and the healthcare landscapes – which are increasingly overlapping – and of the broader governance processes and structures by which these landscapes are managed (Lyll, Papaioannou and Smith, 2009; Tömmel and Verdun, 2009).

In this paper, we are concerned with regulatory vacuums and the subsequent production of regulation in middle-income countries (or emerging jurisdictions) over which there has been limited attention, namely Argentina and India. The former was the subject of an ESRC-funded project called ‘Governing Emerging Technologies: Stem Cell Research and Social Values in Argentina’ (GET),³ which gathered qualitative data around key issues of ‘regenerative medicine’ research governance in Argentina, particularly the role of regulation in facilitating research and the values that should underlie that regulation.⁴ The latter was the subject of an Innogen-hosted project called the ‘Medical Device Project’ (MDP),⁵ which investigated key factors hampering development in India’s medical device industry (MDI), exploring in particular the role of regulation in the effective diffusion of technology.⁶ In short, both projects focussed

or processes within a firm, sector, region, or globally. Transistors and integrated circuits are examples of innovations which caused creative destruction and shifted how actors provide products and offer services.

² The impact of government investment and regulation can be observed in the case of the pharmaceuticals industries. In 1880, Germany and Switzerland were at the forefront of drug development and manufacturing. The outbreak of World War II, however, prompted the US to foster massive chemical analysis and commercial production techniques (Henderson et al., 2007). The resultant system significantly improved productivity, and it provided the platform for the US to leapfrog European pharmaceutical companies.

³ See <http://www.law.ed.ac.uk/ahrc/esrcvaluesproject/>.

⁴ The term ‘regenerative medicine’ refers to that interdisciplinary ‘field’ of research and clinical applications focused on the repair, replacement, or regeneration of cells, tissues, or organs to restore function caused by disease, defect, injury, or ageing. It relies on multiple converging (and emerging) technologies to move healthcare options beyond traditional therapies, and specifically into approaches that rely on or support the body’s own healing capacity. Component technologies include gene therapy, stem cell therapy, and tissue engineering (Daar and Greenwood, 2007).

⁵ See <http://www.innogen.ac.uk/people/Dinar%20Kale>.

⁶ The term ‘medical devices’ captures both simple and highly sophisticated equipment (e.g., everything from tongue depressors, medical gloves and bandages, to surgical lasers, pacemakers, dialysis machines and heart valves) (WHO, 2010). In contrast to ‘medicinal products’, whose primary mode of action is metabolic, immunological, or pharmacological, ‘medical devices’ are instruments, implants, or machines intended to be used,

on fields which are driven by innovation and which are dramatically realigning healthcare and industry practices not only in the subject jurisdictions but around the world. While they were not designed or conducted as a 'pair', they are appropriately considered together because both were informed by the broad relationship between innovation and governance, both reflect a desire to better understand the formation, design, and impact of regulation, and both investigate stakeholder activities and concerns around health-related innovation through empirical research within that emerging jurisdiction.

In the following pages, we introduce the projects that underlie the case-studies, first describing their objectives and methodologies, and then summarising the backgrounds which informed them. We then offer our findings, structuring the discussion around some key issues, namely current regulatory shortcomings and consequences, regulatory objectives or ambitions, and identification of standards. We conclude that regulation can be a boon rather than a burden for a host of reasons only peripherally relevant to risk (which is the most overwhelmingly common driver of regulation). The case-studies also support the conclusion that these jurisdictions (and other similarly situated jurisdictions confronting challenges quite different from those in developed countries) should make every effort to avoid recreating the 'should we / shouldn't we' debate about regulation. Favouring collaborative regulatory design over this dead-end debate could open opportunities to explore new and smarter forms of regulation which might better generate improved bioscience innovations and medical interventions. Before we turn to the case-studies, however, we articulate our concept of regulation, and the nature of the debates that have characterised its evolution.

2. Regulation

The concept of 'regulation' is not uncontested, and the range of instruments and actions caught by the term can expand or shrink depending on the specific definition adopted. We view regulation as a process involving the sustained attempt to control, order or influence the behaviour of actors so as to produce identified outcomes. These outcomes *should* be closely tied (or rationally connected) to the means supported by the regulation for generating influence. While it is possible that a single actor could define all of the key objectives and all of the necessary influence-generating roles and powers to pursue them, such will be extremely rare; many fields, including the technologies innovation and healthcare fields, have very diffuse or 'decentred' operational environments; environments that exhibit characteristics that can frustrate the smooth transformation of policy intent to lived reality, namely complexity, fragmentation, and interdependence (Black, 2001).

With respect to complexity, social problems are caused by many interacting factors, not all of which may be known, the nature and relevance of which may shift over time, and the interaction between which will be imperfectly understood. Additionally, interactions between relevant actors and networks are complex and dynamic because of diverse and shifting interests, objectives, powers, and norms; many actors relevant to a problem will develop autonomously and their behaviour will not remain constant, making interactions hard to

alone or in combination, for one or more specific purposes such as diagnosis, prevention, monitoring, treatment, or alleviation of disease (Shah and Goyal, 2008).

predict and hard to manage (Black, 2001). Moreover, new stimulants (including the introduction of regulatory instruments) will produce behavioural changes, some unintended, that will be uneven across different actors, thereby adding to the fragmentary nature of the environment.

Second, both knowledge and power/control are fragmented. Knowledge fragmentation is more than just information asymmetry, although that persists. Rather, it is a recognition that complex and dynamic problems require more knowledge than any one body can have, and no entity has either the breadth of vision necessary to employ all relevant instruments to their maximum effect, or the power necessary to wield them all even if they had the sufficiently broad perspective (Black, 2001). Power is also fragmented or dispersed, and regulation occurs in many locations and fora, a natural consequence of regulation relying variously on international treaties, agreements and declarations, national legislation and derivative statutory instruments, industry and professional guidelines or codes, and the evolving norms of established and emerging actor networks. The courts are also important regulatory institutions, with the ability to shape sectors; the US Supreme Court's decision in *Diamond v Chakrabarty*, for example, has been credited with a significant role in the rise of the biotechnology industry.⁷

Interdependence describes the reality that, despite some (though differing) levels of autonomy, actors – both public and private – are interdependent (Black, 2002). And these actor relationships, which are often symbiotic, are not always bounded by jurisdiction. As such, regulation is increasingly performed as a multi-directional, iterative interaction between actors, some of whom may sit out-with a jurisdiction. No single actor has ready access to all the information necessary to make informed decisions, nor the authority to direct all of the (other) actors in the field toward optimal outcomes (as defined by that body). Indeed, many may not even be aware of all the regulation that bears on the broad undertaking that comprises a particular field. Ultimately, each actor introduces problems/needs and each actor has capacities and potential solutions, and in this 'messy' way regulation is co-produced (Black, Lodge, Thatcher, 2005).

All of this means that the environment in which decision-making and/or behaviour-shaping authority is exercised is spread amongst actors of very different kinds with varying perspectives, some of whom will have very limited remits and diverging agendas. In both the biotechnology and healthcare contexts (both of which rely on innovation), the most common and widely shared objectives (or desired policy outcomes) are to (Hood et al., 2001):

1. develop products that are safe, effective, and supportive of improved individual and public health outcomes;
2. stimulate inventiveness and growth, particularly in the life science and health sectors;
3. create institutional functions that are flexible enough to accommodate sectoral evolution

⁷ That case involved a patent claim on a genetically modified, oil-eating bacterium. The US Patents and Trademarks Office (USPTO) rejected the claim on the basis that subject matter (a living organism) was a discovery, not an invention. The Court reversed that ruling and granted the patent, thereby establishing the practice of making very broad patent claims which positively encouraged investment (Merges and Nelson, 1994).

without admitting of substantial practice gaps;

These objectives are usually achieved through the following regulatory actions, many of which will have some foundation in legal instruments:

1. standard-setting (establishing permissions and constraints to encourage preferred social states);
2. information-gathering and/or monitoring (producing knowledge about the existing or evolving state of play); and
3. behaviour-modification (changing the state of reality by changing the way relevant stakeholders act through incentives and/or sanctions).

However, as a result of the expansion, transformation and intensification of the risks associated with the biosciences (a claim often tied to the increased power of their interventions into the human body and the environment, and the effect these interventions can have on personal identity, social relations, habitat, climate, and production), their regulation has become extremely politicised. Demands from different actors, which are sometimes almost diametrically opposed (e.g., some desire enhanced research freedom and actor autonomy, while others demand strict prohibitions and clear boundaries), mean that clashes are experienced over what research streams should be publicly funded or even permitted. In this regard, the policy debates that both preceded and followed the adoption of the EU Biotechnology Patenting Directive, for example, are instructive (Harmon, 2006; Harmon, Laurie, Courtney, 2012).

The result is that concerns abound about the regulatory regimes that prevail and about their effect on both the bioeconomies and the healthcare services that are emerging. The form, scope, and stringency of regulation, and the actors who have had a hand in making it, have been much discussed and much maligned, most particularly in developed countries like the UK and USA. Many regulatory efforts, particularly the top-down command-and-control ones, have been reactionary (Laurie and Harmon, 2014), and have therefore fallen short of delivering all that might be expected of 'good regulation'. The unfortunate consequence is that regulatory efforts have been cumulative and non-integrated, thereby complicating rather than elucidating innovation systems and product pathways. A common outcome is that innovation is not facilitated, an shortcoming that is exacerbated by changing regulator attitudes and behaviours (Wolf and Delgado, 2003; Schellekens and Moors, 2010).⁸ Some widely agreed criticisms of bioscience regulation include the following:

- There is too much regulation, resulting in 'regulation overdose' (Espein, 2006) or 'over-regulation' (Havinghurst and Richman, 2006).

⁸ With respect to changing attitudes and behaviours, note that both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have gradually shifted from being post R&D evidence evaluators to active participants in the scientific process.

- There are excessive documentary demands made by regulation, resulting in increased service delivery costs (Curtis and Schulman, 2006).⁹
- There are unanticipated (but anticipatable) and sometimes irreconcilable conflicts with respect to mandated standards and socio-political expectations caused by regulatory interventions in one area (or in one aspect of innovation), resulting in uncertainty and duplication of effort (PWC, 2002; Reed et al., 2006; Munos, 2009; Schellekens and Moors, 2010).
- There are regulatory barriers to 'out-of-the-box' or 'blue sky' thinking, which stifles creativity and therefore prevents disruptive technological improvements (Curtis and Schulman, 2006).¹⁰

To these we might add the observation that, as technologies evolve, regulation (especially specialised or highly specific or targeted regulation) quickly becomes obsolete, so rules designed to protect subjects may develop unintended consequences such as preventing the deployment of alternative products.

As one can imagine, the oft-repeated view is therefore that regulation hampers innovation and the development of strong and competitive industries (Zerhouni, 2005; Reed et al., 2006; Munos, 2009). This view combined with risk-based calls for improved or tighter regulation has pushed high-income countries to oscillate between tight regulation and deregulation (or regulation and reregulation). Of course, while we do not dispute the potential of regulation to serve undesirable ends, that is not the whole story, and regulation need not be just about barriers, boundaries, and sanctions. Regulation can have many salutary effects, some of them surprising, so neglecting to regulate, or deregulating where frameworks already exist, is almost never the intelligent way forward. This is a fact that is not always appreciated in either jurisdictions with sophisticated (or burdensome) regulatory infrastructures, or in developing jurisdictions which emulate those first-movers.

The case-studies below offer a view on the state of regulation in two different but not unrelated sectors from two middle-income or developing jurisdictions. While the sectors and jurisdictions are obviously shaped by different actors and cultures, combined they suggest

⁹ A complaint that has been levelled at the FDA since at least the 1970s (Grabowski, Vernon & Thomas, 1978).

¹⁰ Curtis and Schulman (2006) argue that disruptive innovation is more likely in weakly regulated markets because lower standards allow the introduction of experimental products that cannot meet the 'ideal standards' often erected in more sophisticated regimes, which tend to be more stringent; 'ideal' rather than 'optimal' standards, it is claimed, hamper disruptive innovation. The information and communication technology sector is a good example of this. In the last two decades, the lightly regulated ICT sector has experienced much greater growth and product (and technical) evolution than the much more heavily regulated life sciences sector, and innovations have often emerged from small start-up companies which are able to build resources and upstage existing industry players by innovating in ways that challenge the status quo. In short, less burdensome regulation has facilitated the entry into the sector of new and dynamic players who have gone on to drive the sector forward. By contrast, the life sciences sector is dominated by a relatively small group of multinational companies with the capacity to navigate the regulatory forest. See Tait (2007) and Tait et al. (2007).

insights as to why regulation may be warranted, and they offer lessons that are useful to others acting in these fields, including those in developed or high-income countries.

3. Case-Studies

a. Argentina and the GET: Social Values Project

Argentina faces a collection of healthcare innovation challenges, some of them common to emerging countries, and some less common. With respect to the former, access to healthcare is extremely uneven, healthcare standards are neither uniformly defined nor universally applied, researchers struggle for enough funding to be internationally competitive, basic research has no explicit domestic boundary-setting regulation, and the boundaries between clinical practice and research, and between established therapies and experimental therapies are unclear (Arzuaga, 2011). With respect to challenges somewhat more unique for an emerging country, Argentina experiences significant medical tourism, and conducts high levels of medical research, which might come as little surprise given the strong bioscientific heritage enjoyed by Argentina and the generalised esteem to which scientists are held there (Kramer, 1996; Stekolschik et al., 2010). Indeed, Argentina aspires to make biomedical research a pillar of sustainable development (Declaration of Buenos Aires, 2005; Harmon, 2008). There are now some 45 groups, both public and private,¹¹ conducting research in different branches of medicine, with a significant number of them undertaking work in regenerative medicine (Arzuaga, 2014). GET engaged with key stakeholders in the regenerative medicine setting at a time when regenerative medicine was high on the Argentine policy agenda and significant effort was being expended in exploring the possibility of regulating this field through a command-and-control governmental instrument.¹²

b. India and the MDP

In 2008, the global medical device market was valued at US\$210 billion, and it has grown at a rate of 6% annually since 2000 (WHO, 2010). The US remains the largest consumer of medical devices, with a market valued at over US\$100 billion, though both the Chinese and Indian markets are growing in importance; India's market is estimated at US\$2.75 billion, with growth coming from the expanding middle class of 300 million people with disposable income and heightened health expectations. The US and EU manufacture the majority of all medical devices, and over 70% of the 14,000 devices used in India annually are imported from

¹¹ The most prominent research institutions are the Schools of Medicine and Biological Sciences at the University of Buenos Aires, the Fleni Institute, the Italian Hospital, the Leloir Foundation, the Favaloro Foundation, and the Austral Hospital.

¹² The project ran from 2008-2010. According to the Health Committee of the Chamber of Deputies, the Bills introduced in the National Congress from 2005-2010 included the following: Clinical Research with Drugs, Medical Devices, Biologics, Gene Therapy and Cell Therapy; Code of Ethics for the Promotion of Medicines (2008); Ethics in Health Research: Arrangements; Creation of a National Council on Bioethics; Research, Development, Design, Production and Access to Medicines for Children: Arrangements; Legal Regime Applicable Biomedical Research; National Bioethics in Research and Health Care in Humans (Pertino and Barousse, 2011).

developed countries, especially the USA, despite the fact that there are almost 700 Indian device manufacturers (NIPER, 2010; Kamath, 2010). US and EU regulation is aimed primarily at limiting and managing risk, and it has had a significant impact on the production and diffusion of devices (Foote, 1992). In both cases, regulation addresses risk by categorising devices and inquiring after quality and safety through criteria such as degree of invasiveness of the device, duration of contact with the patient, affected body system, and local v. systemic effects (Kramer et al., 2010; Altensetter, 2010). These standards, combined with the operation of product liability and compensation legislation, have been particularly influential (Shah and Goyal, 2008). While the two regulatory regimes differ in a range of respects (e.g., the EU system, it has been argued, gives the manufacturer primary responsibility over quality, safety, and efficacy in most circumstances, which, in turn, has led to faster approvals (Ramchandran, 2004), but which has been blamed for an erosion of protection of the public interest due to conflicts of interest and lack of transparency (Kramer et al., 2010)), they demonstrate how regulatory systems must serve multiple ends if they are to be effective. The MDP was intended to trace the development of medical device innovation in India and explore the consequences of the regulatory choices that have been made.

c. Common Methods and Joint Questions

In both case-studies, semi-structured qualitative interviews lasting from 50 to 90 minutes were undertaken, dependent on the participant's availability. For the most part, open-ended questions and a relatively informal interview schedule were used to encourage participants to speak in their own words about their experiences, observations, opinions, and desires. Nonetheless, some structure was observed insofar as the investigators ensured a consideration of certain broad topics, and topics were consistently broached in the same order, unless a particular exchange intervened to make an issue's immediate exploration more appropriate/convenient. While both case-studies capture important new evidence pertaining to their subject fields, the opinions of the broader (lay) public were not solicited and the data generated cannot be said to represent either the 'Argentine' or the 'Indian' view.

In GET, those originally viewed as most likely to influence the nature and content of bioscience and stem cell research regulation were targeted. Twenty-two respondents falling in two broad categories took part. Approximately half were regenerative medicine clinicians and/or researchers, many of whom also held policy advising positions, and the other half were national regulators, jurists, and politicians, many of them either scientifically or legally trained. The MDP engaged with four medium-sized firms involved in developing products such as heart valves, orthopaedic implants, and blood bags, and the Sree Chitra Research Institute, which is involved in the Indian medical devices sector. Ten semi-structured interviews were undertaken, with two interviews per company. Interviewees were primarily the Head of R&D and the CEO or Managing Director of the firm. Interviews were also conducted with a senior journalist and industry association president so as to obtain data from other stakeholders. In both case-studies, the original sample was supplemented by further participants through a snowball technique reliant on the social/professional contacts of the original sample.

The transcripts and interviewer notes were (separately) coded and analysed for emergent themes informed in part by innovation systems literature, and then the findings of

each case-study were compared with respect to their engagement with the following questions:

1. In what ways are the prevailing regulatory frameworks deficient (having reference to the regulatory objectives and actions mentioned above)?
2. What are the perceived consequences of these deficiencies for stakeholders on the ground, most notably researchers/innovators and patients?
3. What values and/or aspects of practice should be included in regulation?

The engagement of these questions with the combined data provide the case-studies with a broader base for saying something about the regulation of life sciences and their markets in emerging jurisdictions, and the following analysis is structured to highlight shared insights and points of comparison. Quotes used were chosen as representative of the evidence on the particular issue explored.

4. Findings

a. Deficiencies in Objectives

Regulation should have clear objectives, and the most common ones in the broad healthcare setting are to develop practices and products that are safe, effective, and supportive of improved individual and public health outcomes, stimulate inventiveness and growth, and erect institutional modes that are flexible enough to accommodate sectoral evolution. Regulatory actions to realise these objectives include standard-setting (establishing permissions and constraints), information-gathering (monitoring), and behaviour-modification (through incentives and/or sanctions). We concede that the rational and balanced pursuit of these aims in *high-income* countries is curiously rare, and this is especially so in the biosciences where existing regulation often represents either knee-jerk responses to specific incidents that have exorcised the public,¹³ or over-reliance on the narrow perspective and ambitions of very few the interested stakeholders.¹⁴ While regulatory capacities might exist, they are not uniformly exercised, and they are often spread across multiple bodies, leading to inaccurate understandings of the state of affairs and inefficiencies in responding to developments. How have Argentina and India fared?

i. Regenerative Medicine in Argentina

The Argentine regulatory framework applicable to health research and healthcare is a mosaic of general legislation and more specific administrative rules issued by the Ministry of Health (MOH) and its regulatory agencies. However, the rise of regenerative medicine – and the

¹³ An allegation levelled against the adoption of the *Human Tissue Act 2004* in the UK.

¹⁴ An allegation levelled against medicinal products regimes in relation to the pharmaceutical industry.

proliferation of difficult-to-categorise cellular therapies – prompted the adoption of a host of new regulatory instruments.

First, Executive Decree 200/1997 was issued. Aimed at defending human dignity and controlling activities associated with cloning, Decree 200/1997 merely states that ‘all cloning experiments related to humans are prohibited’. It is silent on all other matters relating to regenerative medicine, and it makes no provision for monitoring the field or sanctioning those in breach. As such, while its one objective is clear (prohibition of reproductive cloning), it provides no substantive guidance or measures for enforcement.

Of greater significance is the *Transplant Act 1993*,¹⁵ which establishes the Central Institute for Ablation and Implantation (INCUCAI) to oversee the transplantation into humans of whole organs and of hematopoietic progenitor cells (from bone marrow and from umbilical cord and placental blood).¹⁶ MOH Regulatory Decree 512/1995 states that any practice involving implantation of non-hematopoietic progenitor cells into humans is an ‘experimental practice’ until it is established that it is safe and effective. In 2007, the MOH issued Resolution 610/2007, which recognises INCUCAI’s competence to deal with activities related to the use of human cells for implantation in humans, thereby empowering INCUCAI to regulate regenerative medicine more broadly (i.e., to regulate cellular research and therapies outside the hematopoietic progenitor cells context).

In response to this, INCUCAI issued Resolution 119/2012, which establishes technical standards and procedures for the collection, processing, storage, distribution, and transportation of cellular products, the aim being to ensure the purity, safety, and efficacy of such products through erection of uniform procedures and controls for laboratories and production centres operating in the field. Preparations are classified on the basis of levels of manipulation, and both measures for handling and prescribed uses are set according to risk (with clinical uses categorised as ‘advanced manipulation’ and therefore higher risk). Standards are enforced through technical inspections carried out by INCUCAI, but it can only act in respect of institutions under national control; it must otherwise act through local health authorities. This, and the fact that only a few protocols have been filed with INCUCAI since 2007 have rendered its standards nugatory.

¹⁵ *Organs and Human Anatomic Material Transplantation Act*, Law 24.193, of 24 March 1993, modified by Act 26.066.

¹⁶ Use of such cells has increased dramatically, which prompted the adoption of the *National Donor Registry for Hematopoietic Progenitor Cells Act 2001*, Law 25.392, by the National Congress and a host of regulations by INCUCAI. For example, INCUCAI Resolution 082/2000 adopts rules for healthcare facilities and professionals intending to collect, cryopreserve, and transplant hematopoietic progenitor cells so as to ensure adequate therapeutic results. INCUCAI Resolution 129/2003 establishes the criteria for the qualification of facilities and teams performing infusion of live unrelated donors. INCUCAI Resolutions 116/2004 and 7700/2004 establish search processes and special procedures so that Argentine patients needing such transplants could search sources out-with Argentina. INCUCAI Resolution 319/2004 establishes rules for banks sourcing hematopoietic progenitor cells from umbilical cords and placentas. INCUCAI Resolution 52/2006 establishes the tariff values for billing procedures for searching international records of unrelated donor. INCUCAI Resolution 309/2007 classifies different uses of hematopoietic progenitor cells based on clinical indications for purposes of characterising them as ‘standard practice’ (and so outside the ‘experimental practice’ rules). INCUCAI Resolution 069/2009 regulates the activity of cord blood banks and the use of cord- and placenta-derived tissue for possible autologous use (i.e., use of the child who was the subject of the pregnancy), addressing collection, processing, storage, research, shipping, and transplantation, and penalties for breach.

In Argentina, medicinal products are governed by the *Medicines Act 1964*.¹⁷ Article 1 states that the Act governs the importation, exportation, production, manufacture, processing, commercialisation, and interprovincial trade of drugs, chemicals, reagents, pharmaceutical forms, medications, diagnostics, and other products used for application in human medicine. It sets standards to ensure the quality and safety of medicinal products authorised for human consumption, erecting civil and criminal penalties for non-compliance (Agosti, 2003).¹⁸ Given that regenerative medicine therapies do not neatly fit into existing legislative categories, the MOH tried to establish a registry for cellular therapies through the National Administration of Drugs, Food and Medical Technology (ANMAT). ANMAT Resolution 7075/2011 defines 'biological medicinal products' as products derived from living organisms or their tissues, and so categorises cellular therapies as Advanced Therapeutic Medicinal Products (ATMPs), which, under ANMAT Resolution 7729/2011, must be registered with the National Drugs Registry for approval for use in humans under the existing regime.

Of a more general character, the MOH issued Resolution 1490/2007, which is intended to standardise activities related to clinical trials in humans to ensure respect for ethical values and human rights. Addressing (1) principles of good clinical practice, (2) research ethics committees, (3) responsibilities of researchers, (4) responsibilities of sponsors, and (5) use of protocols, it draws on the Nuremberg Code (1949), the Helsinki Declaration (2004), CIOMS Guidelines for Medical Research Involving Human Subjects (2002), and other international instruments. In 2011, the MOH reviewed Resolution 1490/2007 and, through Resolution 1480/2011, extended its scope to all research on human health, creating the National Register of Health Research in the process, a system aimed at consolidating information and facilitating public access to that information (Arzuaga, 2012).

Despite considerable regulatory construction, much of it in response to the specific challenges of regenerative medicine, Argentina's system remains sub-optimal. It is surely (appropriately) aimed at developing products that are safe, effective, and supportive of improved health, and also at stimulating innovation and growth, two of the three core objectives identified. Additionally, it has (laudably) set standards informed by respected international instruments, established some limited means of information-gathering through its registries, and extended behaviour-modifying sanctioning to its agencies. However, much of the reform has comprised ad hoc alterations to the duties of existing agencies and the adoption of additional legal instruments, leading to the regulatory complexity and actor burden that is so much maligned. And despite this accumulation, significant regulatory gaps persist (Harmon, 2008; Harmon, 2011).

For example, Argentina is still without universally applicable standards; INCUCAI and ANMAT (whose expertise and the effectiveness of their enforcement mechanisms have been questioned (Arzuaga, 2012) have limited reach into the provinces, which have primary jurisdiction over health, but also a distinct inequality in both financial capacity and attention to

¹⁷ *Commercialization Regime of Medicinal Products Act*, Law 16.463, of 8 August 1964, and Decree 9763/1964.

¹⁸ Again, where medicinal products are not intended for interprovincial transit, import, or export, provincial medicines legislation applies.

research and healthcare demands.¹⁹ Consider ANMAT Resolution 7075/2011, Article 3 of which excludes from its remit biological products made entirely by a specialised centre licensed by a competent health authority to be used in and by that centre under the conditions that the authority has determined. The fact that cellular therapies made and used within a single institution need not be recorded, and will be unscrutinised by either INCUCAI or ANMAT (and so will not be subject to the principles and standards they have erected) have led to suggestions that this lends the administration of unproven cellular treatments some semblance of legality (Bergel, 2009; Arzuaga, 2012). Ultimately, significant research and most clinical applications of regenerative medicine fall outside the regulatory framework and are invisible to any formal or effective oversight.²⁰

ii. Medical Devices in India

Originally, and for a long time, India's MDI suffered from regulatory neglect. The consequences of this were threefold:

- Ignorance: There was little reliable information on device function and performance available to healthcare authorities or practitioners. The only available information was manufacturer marketing propaganda. Devices were sold without any monitoring by authorities or reporting by hospitals.²¹
- Variable Quality: Lack of oversight opened the door for spurious local operators flogging low-quality goods or counterfeit devices made from scrap material. Small trading companies importing from China, Korea, and Taiwan mushroomed. One respondent in the MDP, a CEO of an orthopaedic implants company, reported that his company lost more business to these spurious traders and counterfeit manufactures than to multinational corporations. Even well-known foreign multinationals would 'dump' devices in the Indian market. For example, in 2004 the state-run JJ Hospital in Mumbai used Axxion drug eluting stents manufactured by Netherlands-based Occam despite those stents not having been approved for use in the Netherlands. After patients were harmed by the devices, the government shut down both the Mumbai-based importer and a local stent company, the latter who initiated a judicial review of the decision in an effort to showcase the absence of rules (Magotra, 2006). Even when legitimate and conscientious domestic manufacturers

¹⁹ Regulation exists in some provinces, although approaches vary between legislation and administrative rules. The provinces that have legislated are Córdoba, Buenos Aires, Buenos Aires Province, Tucuman, Neuquén, Rio Negro. Provinces that have issued administrative rules are Mendoza and Jujuy.

²⁰ Quite aside from this, there is a very strong argument to be made that regenerative medicine research and cellular therapies deserve their own sui generis regulatory framework with experts to manage it. Thus, instead of two frameworks relevant to healthcare research – medical devices and small molecule pharmaceuticals – there would be three, thereby allowing them to be tailored to the very different mechanisms on which they rely and the very different challenges and risks they represent. Such specialisation of frameworks would allow better flexibility within them to more seamlessly keep up with technological innovation.

²¹ Thus, for example, when Boston Scientific and Johnson & Johnson withdrew their stents worldwide in 2004, there was no information available in India on how many of these devices had been used or how many adverse events had been reported (Harper, 2003).

entered the market, an absence of uniform quality and performance standards meant that they had nothing to work toward, which contributed further to variable quality, and hampered entry of Indian manufacturers into international markets.

- **Predatory Pricing:** As the clinical community became more averse to using Indian devices, multinationals, who offered no evidence of their production costs, were able to charge high prices for their more stringently regulated and reliable products. Of the more than 11,000 valve procedures performed annually in India since 1994, only 1,000 valves developed by Sri Chitra Research Institute (a leading Indian institute) were used even though they cost less than 50% of the average imported valves (Murthy, 2004). One respondent in the MDP, a leading cardiovascular surgeon, admitted to be compelled to import 90% of the high-end devices for his hospitals at high cost and to replace them every 3-5 years at still higher cost, both of which push up the cost of specialised care making them inaccessible to about one billion patients.

The above-mentioned *JJ Hospital* case resulted in the High Court ordering the government to set standards for the import, manufacture, sale, and distribution of devices. In response, the government amended the *Drugs and Cosmetics Act 1940* (D&C Act) and the *Drugs and Cosmetics Rules 1945* (Rules) to cover ten specific medical devices. The primary objective of the D&C Act, which is administered and enforced by the Drugs Controller General of India (DCGI) and the Central Drugs Standard Control Organisations (CDSCO), is to promote safe and effective healthcare by regulating the import, export, manufacture, distribution, and sale of drugs, cosmetics, and (now) devices.

The D&C Act now covers specified devices intended for internal or external use in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals (although no generalised risk classification is erected). It establishes a structure that contains control points at the levels of market, manufacturer, and healthcare institution. Although authority is shared with state Licensing Authorities (responsible for monitoring drugs and devices moving in the market), and state Inspectors (responsible for market surveillance by drawing samples from retailers, hospitals, and manufacturers), the CDSCO is responsible for overseeing medical device and diagnostics firms and for disseminating information on registered devices and drugs, licensed distributors, and compliance. Imported devices must be approved for sale in the country of manufacture, and importers can rely on US, EU, Japanese, Canadian and Australian approvals for proof of quality, safety and efficacy (i.e., this fast-tracks device approval). Where no such registration exists (such as when the device is domestically manufactured), the device must receive an ISI Mark from the Bureau of Indian Standards. Schedule 'M' of the D&C Act articulates good manufacturing practices, and specifies requirements for premises, equipment, personnel, storage, documentation, etc. Manufacturers are required to comply with Schedule 'M' under the conditions of their license.

Patients, healthcare providers, and domestic device manufacturers are all expected to benefit from these amendments, which should, it is assumed, make it difficult for counterfeiters and low-quality importers. They also benefit from the clarity offered by the guidelines for authorisation of devices, and this, it is felt, creates the opportunity to develop devices that can compete with products from foreign multi-national corporations.

b. Consequences on the Ground

The above demonstrates that, while not necessarily optimally arrived at, the Argentine and Indian frameworks do articulate to some degree the baseline objectives one would hope and expect to see in the health context. That is, their genesis is in concerns for patient safety and the provision of effective healthcare, and, additionally, for domestic technical innovation and economic growth (admittedly not comfortable bedfellows). Flexibility has not been a key feature of either regime. However, reform efforts have introduced some responsiveness to changing circumstances. So how well have they achieved their objectives?

i. Risk and Exposure in Argentina

GET exposed evidence that the complex of regulatory instruments comprising the Argentine regenerative medicine framework is failing to achieve two highly valued objectives:

- realisation of safe and effective science and healthcare; and
- encouragement of scientific innovation and economic growth.

Importantly, it was not felt that these objectives are disregarded by the framework or those administering it, but rather that not enough attention has been paid to achieving them through rationally connected measures. In short, it wasn't an absence of salutary objectives that rendered the framework ineffective, but rather an absence of any truly effective modes of operation (e.g., articulation of standards, monitoring of conduct, and authority to change behaviour).

First, and most importantly, it was felt by most respondents that the framework, considered holistically, had little chance of effectively encouraging (much less realising or imposing) safe healthcare, or rather the honest and good-faith delivery of proven and effective clinical tools and practices. Many respondents opined that the general lack of systematic monitoring of either scientific or clinical practices meant that improper practices went unidentified, and where they were known or suspected, they went unchallenged and unpunished with the result that patients were vulnerable to a variety of harms resultant from acceptance of poor interventions administered by questionably motivated professionals. While it would take a bold (and misinformed) person to suggest that regulation guarantees 'good science' or 'good clinical practice', and while it was acknowledged (at least by some) that consistently achieving these requires systemic approaches, it was generally held that regulation is one of the most important elements of discouraging 'bad science' and 'bad clinical practice' (eg: falsifying results, fraudulent behaviour, improper claims about the utility of interventions, administering highly experimental treatments).

For example, respondents identified ample scope for actors to behave in ways detrimental not only to patient safety but additionally to the scientific undertaking. R5, a stem cell researcher, observed that clinical trials have been undertaken (and published in international journals) without the consent of authorities as mandated by MOH rules, and an absence of monitoring leaves such breaches unrectified:

So the scientific community should be much more strict on asking, for example, for the authorisation to do the clinical trial ... because if that paper gets published then, for us in Argentina, it is more difficult to tell the patient, 'This clinic is doing something wrong'. Because the clinic then shows the scientific paper saying this clinical trial is validated.

Thus, this respondent felt that more comprehensive coordination is warranted. R6, a public health physician and policy advisor, stated:

You have problems in the academic institutions [and] with ethics committees. ... Then you have problems with investigators. I [know an] Argentinean investigator, he knows nothing about the international regulations.

R19 added:

You know that we have some places in Argentina – like St Nicholas in the province of Buenos Aires – that are using cellular therapies for everything. And that is, they have protocols that ... don't have the approval of the Ministry of Health, and they don't have the approval of INCUCAI. And they publish papers in the international level, because, I don't know why, because ... in the paper they have the [assent of the] institutional review boards in their institution. And so they have the informed consent of the patient because the patient is blind. And of course, the journals accept the papers.

In short, respondents acknowledged the risks to patients associated with this research and the application of its outcomes, and considered government regulation to be an important but currently absent shaper of behaviour and guarantor of quality. The prevailing situation permitted actors to behave according to their own values and interests, which did not always support the realisation of public goods. From a scientific perspective, they contributed nothing to knowledge, which undermines the justification for research, and from a healthcare perspective they offered no demonstrable clinical effect for patient, or, worse, distracted patients from getting alternate and proven therapies that would have an effect, a scenario which destroys the reputation of scientific research and conscientious healthcare providers. And it has been reported that, despite INCUCAI's licensing power, unproven stem cell treatments continue to be administered (Arzuaga, 2014).

The second unmet objective was the aim of facilitating science and innovation and thereby encouraging not only economic growth, but the growth of knowledge with the potential for translation into appropriate clinical interventions. Respondents felt that researchers operating in potentially high-impact but also highly politicised fields such as regenerative medicine were offered no 'regulatory cover'. By-and-large, researchers wish to (1) pursue their science, and (2) where appropriate, engage with publics around their science and its trajectories and potential outcomes. The former is the natural desire that pushes researchers to enter and then excel in their chosen field. The latter comes from the realisation

(by some) that both public understanding and acceptance of bioscience *and* its outcomes are improved when science is approached democratically, that is pursued in an open and participative manner. These values of openness and discursiveness are particularly challenging in Argentina because of the perceived antagonism of certain institutions toward science generally and regenerative medicine more specifically. One institution is the Catholic Church.

While there is a risk of broad-brushing away the diversity of opinions toward science within the Church, it can be said that it has acted suspicious of, and resistant to, many aspects and aspirations of regenerative medicine (Macklin and Luna, 1996; Acreo, 2006; Luna and Salles, 2010). This view was widely held by respondents, many of whom viewed the Church, or at least its formal, public positions, as antagonistic. They felt that rigid Church positions and dogma made it impossible to have reasoned and rational public discourses on almost any aspect of regenerative medicine. One respondent, R4, a stem cell researcher, said:

[Y]ou will see that the debates [about] abortion; there are still people who are against abortion and they go to the hospital and try to convince very poor people that they shouldn't abort. It is the claim that God and angels will come and will lead them. I don't know. There is still a lot of work to do.

With respect to stem cell research related dialogues, R16, a physician, stated:

Just within the specific scientific community. In that group we agree this kind of research is important, but there is a problem in Argentina with religion. ... People are confused, confused ideas from church [about] science. ...

R19, a physician, health administrator, and policy advisor, noted:

I am sure that if we put the [issue of embryonic stem cell research] on the face, it's very probable the Catholic Church would take a position against that. And the Church influences, probably not the population, but the politicians.

In settings where powerful institutions are oppositional, or are perceived as such, the science culture and the individual researchers' place within it become negative and embattled. In Argentina and similarly polarised environments researchers are confronted with challenges and concerns that are not necessarily experienced to a comparable degree by colleagues in competing and collaborating jurisdictions. Many of the respondents harboured serious concerns over such basic matters as their 'freedom to research', which they felt was jeopardised by working openly or by publicising their work. This perceived need to conduct science 'behind closed doors' was articulated by R14, a lawyer, who stated that scientists remain reluctant to announce their findings to the people and that this reluctance means that people form decisions about science (and healthcare interventions) based on partial evidence; the scientific voice is not heard so people sometimes form false impressions. R15, an academic scholar and bioethicist, stated:

There [was] some buzz ... when the Obama position about accepting research

with stem cells was brought up by the [Advisory Commission on Regenerative Medicine and Cellular Therapies], but it's more like isolated voices. I think that behind the scenes, the root of the problem is the position of the Catholic Church. And that's why everybody tries to be cautious about what they say and how to deal with this issue. ... It is like everybody is afraid of the Church And so people that are doing assisted reproduction will save embryos and they will not destroy embryos and they will not accept that they do anything. ... And even the abortions that are accepted by law, they are not performed. ... I think there is really a silence about it. ... The researchers are not saying anything. We have really high quality centres for assisted reproduction, and people come to Argentina to do these treatments because they are cheap and very good. But at the same time, nobody will accept what they are doing. ... [N]obody is willing to go upfront and say, 'Well, we do this because it is important,' and it is difficult continuing to work with embryos.

This position was echoed by a member of the Advisory Commission on Regenerative Medicine and Cellular Therapies, who stated that the Commission tried to encourage an open debate on stem cell research in 2007/08, but many stakeholders were reluctant to engage because of concerns about negative attention.

The Argentine researchers who participated in GET wish to be more open in the pursuit of their science. R2, a researcher and regulator, stated that 'proper scientists' are tired of listening to the claims of those who are working unethically, and would like to have better and safer opportunities to clarify the situation. R16 reiterated this, stating that attendees at doctors' meetings claimed that they would like to work in regenerative medicine with more contact with supportive organisations. As it stands, and due to the weaknesses of the regulatory framework, stakeholders are not comfortable exposing their research or announcing their findings publicly because of anticipated reactions from institutions like the Church, and because of potential reactions from publics labouring under misunderstandings of science which are, at least in part, encouraged by the Church.

In summary, the Argentine regulatory framework fails to achieve two of its primary objectives, namely to promote patient safety and to encourage locally useful scientific innovation. Respondents in GET viewed the prevailing framework as unfit insofar as it exposed the two stakeholder groups considered to be most in need of protection (patients and researchers) to multiple risks of harm; it failed to protect patients, who are exposed to inappropriate risks by inadequately scrutinised and often experimental procedures, and it failed to protect researchers, who are demonised by antagonistic interest groups. The consequence was the perpetuation of poor scientific practices and the gagging of ethical researchers.

ii. Confusion and Incompetency in India

The Indian government had two primary objectives in amending D&C Act, namely to promote accessibility to safe and effective devices for the local population, and to protect 'above-board' domestic manufacturers by creating a framework for notified devices. However, it has struggled to achieve these objectives on the ground, in part because of the deficiencies in the regime

created, which is (1) inappropriately aligned, (2) under-inclusive, (3) lacking in effective monitoring.

The regime is inappropriately aligned insofar as it forms part of an existing framework which was designed for very different technologies, namely medicinal products (pharmaceuticals), which are different in nature, action on the body, and packaging. For example, 'sterility' differs in meaning between medicinal products and medical devices; drug manufacturing requires 'clean room conditions' (necessitating certain flooring, air-flow, and energy deployment) whereas medical devices are often sterilised at the point of use. One respondent in the MDP, a leading manufacturer of diagnostic devices, complained:

This industry is considered to be a pharma segment but really does not belong there. The authorities themselves are not knowledgeable about [the] diagnostics industry. A device cannot be regulated as a drug.

Improper fit of concepts has led to interpretational confusion and the introduction into the market of devices varying wildly in quality (WHO, 2012).

Another key shortcoming is that the new provisions cover a small spectrum of specified devices only, ignoring the vast majority of devices on the market. Non-sterile devices, for example, which remain freely importable and sellable in India, are completely invisible to the regulatory framework. This under-inclusiveness has, again, permitted counterfeit and dubious quality devices into the market.

A third critical failing is that relating to the failure to erect a monitoring system for recalled devices. All medical devices carry a certain degree of risk and have potential to cause harm in unforeseen circumstances. If defects are detected during regular use or routine quality inspections, then manufacturers recall the product so as to avoid serious health problems for patients. Foreign multi-national corporations routinely recall products, and with more than 70% of devices in India being imported, the failure to assign responsibility for ensuring that recalled devices do not remain in active use is a major flaw. Risk assessments and recall vigilance are left to healthcare professionals, or to the honesty of manufacturers to pull defective stock of the market.

In addition, the new regime was accompanied by significant uncertainty about its interpretation. Prior to issuance of the MOH's Implementing Guidelines, manufacturers had very little indication of how the regime would be administered. Uncertainty led customs authorities to hold shipments, which created a shortfall of devices and debate on their legal status and inclusion in the D&C Act. Once the Implementing Guidelines were issued in 2006, they suffered from inconsistent interpretation by different regulatory authorities (e.g., customs officials, state drug controllers, CDSCO officials, etc.). State involvement has led to discrepancies in administration between central authorities and states and indeed between states. Some suppliers waited over 7 months for licenses, even for products that had been in the market for more than 20 years and had received regulatory approval in Europe (Kamath, 2007). Additionally, there is a dearth of qualified engineers to head central and state testing laboratories, which has led to mistakes and complaints about quality. A leading manufacturer of diagnostic devices points out:

More than 95% of the quality complaints are due to procedural mistakes. We noticed that the same kits perform very well in the export markets, but get complaints from the domestic market. This gives a major problem for the manufacturers, particularly newer companies.

All of the above has made the Indian clinical persist in its hesitancy to use Indian devices; thus, rather than empowering and legitimating domestic manufacturers, the D&C Act is endangering them. The prominent view is that ‘optimal regulation’ requires a bespoke regulatory body for devices.²² The Indian Medical Regulatory Authority is now intending to create a two-tiered system reliant on third-party conformity assessments through a number of notified bodies analogous to that adopted by the EU (Ramchandran, 2004), but suspicion and poor communication between departments combined with severe infrastructural problems have hindered regulatory development (as well as implementation of existing rules).

In summary, the Indian regulatory framework fails to achieve two of its core objectives, namely to promote patient safety and encourage local innovation and competitiveness. The original regulatory lacunae did nothing to protect patients from injury stemming from devices, particularly counterfeit devices, and the court-imposed bolt-on system has done little better. Local actors still struggle to gain the trust of health authorities, practitioners, and patients, and the government struggles with how to set up a framework that properly distinguishes between medical devices and medicinal products.

c. Elements of Good Regulation

Despite the stark failures of governmental interventions to date, respondents in both GET and the MDP recognised the value of a clear, standards-based, top-down regulatory framework, and most expressed a desire for such a command-and-control instrument. In GET, R10, a legal-ethical academic, stated:

I think that you need to regulate because the power and possibilities in the scientific field are so much, and the possible effects are so terrible With a lot of care ... and consulting specialists, something must be done.

In the MDP, a chairman of a diagnostic firm stated:

I welcome the regulatory system in the medical device market. Laboratories and manufacturers should validate for performance of the product and capability of the technical staff. It will help us to weed out unscrupulous sub-standard devices.

In particular, respondents wanted something that set boundaries, helped to dissuade ‘bad’ operators, and sent unambiguous messages to publics. On the former, in GET, R2, a regulator,

²² As for a process of establishing what ‘optimal’ means, the process adopted by Argentina from 2008-2012 in the regenerative medicines context is a useful model. For an elaboration of this process, see Laurie, Harmon & Arzuaga (2012) and Harmon, Haddow & Laurie (2013).

suggested that regulation must facilitate science while demarcating forbidden pursuits and practices. R12, a federal judge, opined that good regulation which encourages useful outcomes would be helpful. In the MDP, the head of medical device firm suggested as follows:

It is essential that India enact medical device law soon. This would ensure that only products conforming to international standards are made. Counterfeit manufacturers will be prevented from marketing spurious, untested products in unfair competition with authentic manufacturers.

Some respondents suggested that new regulation might lead to a 5-10% increase in the cost of devices, but will be more beneficial in the long-term as patients will trust locally manufactured devices that are certified.

On the related issue of messages sent through regulation, there was a high degree of symmetry in the case-studies. Core propositions can be summarised as follows:

- Regenerative medicine is, in the usual course and where appropriately reviewed and conducted, ethically defensible, publicly supportable, and internationally competent.
- Indian devices are, in the usual course and where appropriately developed and tested, ethically defensible, publicly supportable, and internationally competitive.

In short, they want some formal framework with a legitimating effect, for this, it was perceived, will serve a trust-building function (as between the public and scientists/innovators) that will promote greater transparency, an improved working culture, and improved science/innovation.

But what are some of the key values or elements that were considered essential for good governance? Again, we see similarities in the evidence, for respondents in both case-studies identified 'transparency' and 'innovation' not only as substantive regulatory objectives, but as key elements of the regulatory frameworks. What might these concepts mean for these jurisdictions and beyond?

i. Transparency and Innovation in Argentina

Respondents in GET were concerned that those operating in health innovation and healthcare should be 'transparent', a recurring value which had several overlapping components, including honesty and engagement. All respondents thought that stakeholders must be scrupulously honest with the public and with patients, and they shared a concern that too many people are being led to believe that stem cells, for example, will work through some magic to cure all their ills. R1, a scientist and regulator, acknowledged that too many people lie, promising both patients and regulators one thing and doing something else. In his governance capacity, he reported seeing occasions where researchers take tissue from people for purposes outside their approved protocol. R3, a stem cell scientist, stated that dishonesty is "the enemy [that] we have to fight against."

Linked to these mutually enhancing ideas of transparency and honesty were the joint ideas of engagement and interaction. It was felt that innovators must engage more openly and

consistently with stakeholders. R5, a researcher and ethicist, stated:

It is very important to open the debate and to have opposite visions of the subject sitting at the same table and think that maybe both have rights. That not one has the truth and one has not, maybe both have the truth. You need to really conclude what is the best for the country and for the people of the country. ... The higher consequence of good communication ... is that you don't give a [chance] for so-called doctors to propose therapies that are not validated.

R11, a clinician, stated:

I want social debate about stem cells, but I think this is not currently an agenda of the government. ... We in society need to think, and to express opinions regarding stem cell therapies.

Respondents believed that publics have the right to know the scope and purpose of research, the risks, benefits and expectations associated with research, the interests and potential conflicts of the researcher(s), and 'what is behind the research' (i.e., the source and provenance of tissue). Researchers should be called upon to defend and/or explain their work, and they should be expected to record and make public their work.

Importantly, there was significant agreement that regulation should contain elements that ensured transparency (e.g., honest interactions, open debate, publicly accountable decision-making). So while both the scientific and healthcare communities need to be more careful about what they promise, and researchers need to adopt a more open and participative stance regarding the ambitions and direction of science, these changes could, it was felt, be facilitated by regulation. Additionally, the regulation itself must be more transparent; it must not be too complex so that neither stakeholders nor publics can understand or navigate it.

On the matter of 'innovation', many of the respondents in GET emphasised the need for society to recognise some minimum level of liberty to act (and conduct research) in accordance with one's own feelings and values so long as others were not injured. On this point, R3 echoed a lot of respondents with this observation:

In science, you have to have freedom – academic freedom – to go this way or that way. This is essential to the scientific community. ... [Even for controversial science] I would prefer society to say, 'Well, go ahead and we are going to fund this if you work with peer review ... from the scientific community and accept this common ground. ... I tend to think to be open minded and science needs freedom.

R14, a lawyer and ethicist, stated:

If it is true, that God made us, he gave human beings intelligence to research medicine, biology, and to improve our situation. So I think it is necessary that researchers are given the freedom to develop science.

R20, a lawyer and ethicist, acknowledged the need for freedom, but returned to the idea of society shaping science:

Sometimes people think that if something can be done it should be done. I think that we have to fight that attitude. I do believe that a moral conversation on stem cell research is absolutely necessary. I would not say, 'Yeah you can do it, let's do it,' without even thinking about it, because ... there are too many values and too many aspects involved ...

In essence, it was generally felt that social plurality must be explored, but it must not lead to the lowest common denominator (or the most blandly palatable science). Researchers have a responsibility to take opportunities and to push boundaries, but in the understanding that they have duties to society. Those duties include the obligation to rely on, and to generate, good evidence thereby encouraging scientific veracity, and to abide by reviewed research protocols and internationally informed clinical standards.

And again, regulation was felt to have a direct and important role in achieving good innovation. One respondent suggested the need to begin with science policies, another identified a need to review lab practices, and a third opined that no regulation was better than bad regulation, but most agreed that some regulation for science and innovation was important. R17, a clinical researcher, stated that regenerative medicine must be regulated:

We can't work without regulation. And medical doctors can't work without regulation. And it is not good to work without regulation.

The need for boundaries and guidance alluded to here, and its benefit to innovation, was echoed by almost all of the respondents, but other benefits were also identified. R15, an ethicist, stated:

I think that trying to regulate stem cell research may help also with being more honest regarding other issues. ... I think it is always better to have some kind of regulation, than leaving it like this and everybody free rides.

In summary, transparency and innovation were seen as important social-scientific targets and appropriate subjects for regulation, and transparency was additionally seen as an important characteristic of regulation.

ii. Transparency and Innovation in India

As in GET, the MDP identified transparency and innovation as important components and goals of the regulatory framework. Many respondents pointed out that regulatory structures and conceptions were unclear, in part because of the lack of differentiation between medical devices and medicinal products, and they wished for an autonomous, single-level regulator to govern the sector (because the existing multiple authorities create confusion). A respondent from the Association of Indian Medical Device Industry stated:

The government is trying to say that medical devices are different from drugs, but this Act continues to regulate devices under the category of drugs. And various authorities at centre and inspectors at the state make these things very complicated. A single autonomous regulator under the Ministry of Health will be good.

Respondents believed that to ensure patient safety it is important to have a regulatory framework that engages with manufacturers, vendors, patient groups, local hospitals, and international regulatory bodies. There was significant agreement regarding investing in education and training programmes for users, and awareness programmes for patient groups. One respondent stated:

The key objective is to make sure patients get appropriate treatment. Doctors need to be given training on use of devices and patient should be made aware of risks and quality standards.

The Indian government appreciates the value of recognising devices as a distinct category, and so introduced the *Drugs and Cosmetics (Amendment) Bill 2013* in Parliament in 2014. This Bill articulates a regime more in line with standard international practices developed by the International Medical Device Regulators Forum. However, there remains an issue of appropriateness of these provisions for local contexts and their impact on supporting local innovations. For example, the Bill defines ‘adulterated devices’ as any device that:

- is composed of rusted, corroded, filthy, putrid or decomposed substances;
- is packed under unsanitary conditions that would make it hazardous to someone’s health;
- contains toxic substances.

It then puts responsibility of ‘adulterated devices’ on manufacturers, but it must be recalled that devices have a greater chance than drugs for becoming contaminated at the point of use, well after the manufacturer has relinquished responsibility. It has been argued:

So even if a user stores a device improperly, it’s the manufacturer who will be held liable. That’s not all. The Bill talks about minimum standards for medical devices, but doesn’t actually define what these standards are. These devices are pieces of science and engineering. You can measure the efficacy of drugs, but not of a medical device. The government should measure their performance. Drugs and medical devices are two completely separate things. You can’t measure them with the same indicators (Nagarajan, 2013).

Many respondents felt that confusion has contributed to lack of transparency and poor management, which means that local innovation is still stifled.

On the issue of innovation, it was reported that Indian manufacturers are interested in incremental improvements and adaptation of devices to local settings, which have distinctive

disease profiles dominated by communicable diseases such as malaria and dengue fever. Indian manufacturers are thus focused on developing safe, effective, low cost devices. For example, in 1990, the Sree Chitra Research Institute developed a mechanical heart valve. Developed incrementally, it was a simple mechanical design that was much cheaper than foreign imports. Respondents suggest that, without proper regulatory support and standards, these and other developments will remain unrealised.²³

A new framework, it was felt, must do two interrelated things. First, it must place the concerns of poor patients at the heart of the regulation, taking positive steps to remedy their persistent lack of access to appropriate diagnostic and treatment devices. Second, it must facilitate local innovation by permitting only legitimate devices to be sold in India, and by encouraging trust in local manufacturers. Until this happens does, the 'above-board' domestic devices industry will continue to struggle despite competing against expensive imports and dangerous counterfeits. And to achieve this, consultation with stakeholders (e.g., patient groups, surgeons, scientists, entrepreneurs, hospital authorities, etc.) was cited as an important step in designing a new framework that adequately represented the interests of all stakeholders.

5. Discussion

Despite differences in their factual foundation, a number of findings are supported by our comparative analysis. First, the 'do we / don't we' debates around regulation in the biosciences and biotechnologies sectors are valueless. The risks to both health human and to socially useful innovation are too many and too severe to be left unaddressed by regulatory absence, even in countries with myriad other and perhaps more pressing social concerns. In other words, leaving industry and interested actors to their own devices is not the answer; in the global health and innovation settings, markets neither identify nor consistently correct inappropriate behaviour. Both GET and the MDP uncovered evidence that, when combined with the absence of regulation, the contested nature of an undertaking (regenerative medicine), or the complexity of the knowledge necessary for success (devices), or both, can be critical barriers to innovation and effective uptake of products and practices. Tied to this, the fallout extends to issues such as willingness to invest, development of local technical capability, and ability to plug into global structures.

Second, the quickly evolving, technology-heavy, and internationally networked sectors that are regenerative medicine and medical devices (and to these we might add other health-related sectors and activities) will struggle to meet reasonable socio-political and industry objectives if they are made to rely on a patchwork of existing regulatory instruments, or on instruments forged in a reactionary way. The evolution of both sectors in these countries are characterised by flawed policies which have informed half-measures or bolt-on instruments to existing regimes not at all intended to address them nor adequately provisioned to cope with them. Their deficiencies have resulted in them being met with a great deal of dissatisfaction,

²³ Developments emerging from local technology centres supported by foreign multi-nationals. For example, GE and Stryker each have centres in Bangalore while Stryker, Covidien and Johnson & Johnson have centres in Gurgaon, Mumbai, and Hyderabad respectively.

which can be amplified in emerging countries that have less developed alternative support institutions and networks, or smaller and less diverse funding streams for innovation and healthcare. In adopting a course of reactionary regulatory accumulation, these countries are following the lamentable path of developed countries, and should be cautious about doing so.

Third, bespoke regulation serves multiple ends. In addition to promoting safety and rational risk management, which are key targets for biosciences innovation regulation all around the world, it offers legitimacy, signalling to publics that the undertaking is sanctioned. This, in turn, is seen as having knock-on effects for open science, public debate, and transparent governance. Importantly, however, not just any regulation will do; the failure of the Indian medical devices regulation to raise the quality of domestic devices demonstrates that great care must be taken around regulatory objectives and means if regulation is to deliver on its multiple promises. The evidence from both jurisdictions supports the claim that social objectives and performance standards need to be participatively agreed and clearly identified, oversight must be institutionalised, and correctional authority must be enumerated if the regulated fields are to achieve their potential and not contribute to even greater patient risks.

Fourth, the case-studies support the claim that there is an appetite for (state) regulators to be ‘first movers’ in designing regulation *in cooperation* with key stakeholders. The failure to act in a timely and proactive way has had multiple consequences: in Argentina, it has largely silenced the scientific community in the face of vociferous opponents, thereby surrendering the public discourse to oppositional organisations and to unethical operators offering ill-considered or ineffective experimental treatments; in India, it has opened the market to domestic counterfeiters and foreign devices dumpers, again leaving the patient to suffer the consequences, and regulation fashioned by the courts in the context of a case (rather than by the legislature after due consideration) has proven ill-conceived and ineffective. Adopting a *regulatory agenda* wherein key non-government but intellectually engaged actors are given a role in steering the form and content of the regulation (so that it is sensitive to the needs of the regulated environment) but without turning the undertaking over to those interested stakeholders altogether is an important aspect of achieving jurisdiction-sensitive ‘optimal regulation’. Such can create a more positive environment more conducive to innovation.

Fifth, not only should emerging jurisdictions like Argentina and India eschew the ‘do we / don’t we’ dichotomy, but they should eschew the un-reflexive redeployment of regulation borrowed from other settings or jurisdictions, for these models are likely shaped by very different contexts and experiences. Research has already demonstrated how regulatory systems can motivate particular behaviour patterns among those regulated, which means that context is important (Milne and Tait, 2009; Chataway, Tait and Wield, 2006). In emerging countries such as Argentina and India, regulation might therefore be expected to play a somewhat different (or more multifarious) role than its counterparts in developed countries. Thus, emerging countries should avoid recreating the regulatory complexity, accumulation, and fragmentation that characterises the most likely emulated models (eg: EU or US models), and rather focus on how to achieve more ‘optimal’ and ‘joined-up’ regulation.²⁴

²⁴ We are familiar with the literature around ‘responsive regulation’ (Ayres and Braithwaite 1992), ‘smart regulation’ (Gunningham and Grabosky 1998), ‘problem-centred regulation’ (Sparrow 2000), and ‘really responsive regulation’ (Baldwin and Black 2008) and contend that, to be ‘optimal’, regulation would have to be cognizant of

Regarding 'optimality', they must design regulation that has its own clear social objectives shaped by the specific context in which it is expected to operate, but that is also keenly aware of the other regimes to which actors in the field are beholden. Ideally, the resultant regulation might not rely too heavily on rules, but rather on values or principles and properly supported expert authorities to help industry implement them. Regarding 'joined upness', three issues are pertinent. First, the regulation should be crafted with partner or associated fields (and their regulatory demands and burdens) in mind so as to avoid conflicting standards and reduce the regulatory cost of operating (through duplication of regulatorily-imposed actions). Second, it should be crafted so as to dovetail with international standards and/or systems; it must strive for some level of harmonisation of terms and responsibilities, thereby paralleling the international nature of the science and its markets. Third, it should remain explicitly aware of the stage in the innovation process at which the regulated action sits. Being 'joined-up' in this context means being careful to articulate values commiserate with that stage and setting responsibilities in recognition of those that precede and follow that stage.

6. Conclusions

To conclude, we argue that both sound healthcare interventions and socially useful innovation may be best encouraged through regulatory innovation, and here emerging jurisdictions are in a strong position to 'leapfrog' developed jurisdictions reliant on more entrenched regulatory instruments and pathways. The development of 'optimal regulation' which does not slavishly copy existing models is within the capabilities of emerging countries if they are conscious of the precedents and sensitive to their own social needs. With respect to the former, examples of regulatory innovation which has led to technical innovation include California's efforts around the environment, the US's efforts around orphan drugs, and India's efforts around the licensing of patented medicines. In pursuing this regulatory innovation, international standards have an important role to play, but actors must be cautious about bowing to international *health politics*, and, importantly, regulators must know when to stop 'innovating' and let the system run (Black et al. 2005).

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these theories, each of which has something to contribute, as well as sensitive to the prevailing socio-moral culture in which it is expected to operate.

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